41

THIRD PHASE REPORT

on

AN INVESTIGATION OF THE DYNAMIC BEHAVIOR OF CIGARETTE SMOKE

covering

REVIEW OF LITERATURE ON RETENTION OF AEROSOL PARTICLES IN THE RESPIRATORY TRACT

to

PHILIP MORRIS, INCORPORATED
RICHMOND, VIRGINIA

April 30, 1959

by

R. I. Mitchell

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May 14, 1959

Mr. Frank Resnik, Supervisor
Instruments and Physics
Research and Development
Philip Morris, Incorporated
P. O. Box 3D
Richmond 6, Virginia

Dear Frank:

Enclosed are ten copies of our Third Phase Report on "An Investigation of the Dynamic Behavior of Cigarette Smoke". This report is concerned entirely with the "Review of Literature on Retention of Aerosol Particles in the Respiratory Tract", conducted during January, February, and March, in preparation for the experimental study now under way of lung retention of smoke particles.

The First Phase Report, as you will recall, described the cascade impactor developed especially for determining particle-size distribution of cigarette smoke. The Second Phase Report described refinements in the design of the impactor and summarized extensive studies of particle-size distribution as a function of puff sequence, bulk density, brand of cigarette, casing agent, and extent of coagulation.

The enclosed review of the literature on lung retention of aerosol particles covers the mechanisms of particle deposition, methods of producing experimental aerosols, and theoretical and experimental studies of deposition in the respiratory tracts of both humans and animals. Of special interest is the first figure which shows, schematically, the anatomy of the pulmonary tree and the sizes of particles that deposit in each region.

This survey will be helpful to us as we continue our studies of lung retention of cigarette smoke. We hope that it will also serve your research staff by providing, in convenient form, a further understanding of this important subject.

Sincerely yours,

J. M. Pilcher

J. Mason Pilcher
Assistant Division Chief

JMP:mrm
Enc. (10)

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PROJECT BMI 28-0105

THIRD PHASE REPORT

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Period Covered by Report: January 1 – March 31, 1959

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Author: R. I. Mitchell

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REVIEW OF LITERATURE ON RETENTION OF AEROSOL PARTICLES IN THE RESPIRATORY TRACT

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R. I. Mitchell

INTRODUCTION

The purpose of this report is to review the existing literature dealing with the retention of particulate matter in the respiratory tract with special emphasis on the effect of particle size. Because of the importance of inhaled dust particles as industrial hazards, much study has been made of their injurious effects. Many investigations of pneumoconiosis associated with the mining industry were carried out during the first quarter of the Twentieth Century. Since that time the literature on this subject has become so extensive that much time and space would be required to review all papers dealing with lung retention. The majority of the papers on pneumoconiosis are concerned only with dust loading and not with the particle-size distribution of the dust; therefore, they are of little importance to this survey and have not been included.

During the past few years, interest in aerosol therapy, chemical warfare, and the dangers associated with radioactivity has resulted in numerous papers dealing with the action of inhaled particles. Most of these papers appear to have considerable merit; however, because of differences in the techniques used to determine the retention of the particles as a function of particle size, agreement among the results presented by various experimenters is poor. However, an attempt has been made to evaluate the reliability that can be placed on the data obtained by the various techniques.

The material reviewed in this report was obtained largely from Chemical Abstracts, Archives of Industrial Hygiene and Occupation Medicine, Journal of Industrial Hygiene and Toxicology, British Journal of Industrial Medicine, Journal of American Public Health, and other appropriate medical journals.

The material is reported under the general headings of (1) Mechanisms of Deposition, (2) Methods of Producing Aerosols for Experimental Studies, (3) Theoretical Studies of Deposition in Man, (4) Experimental Studies of Deposition in Man, (5) Experimental Studies of Deposition in Animals, (6) Summary of Results, (7) Possible Application of Lung-Retention Survey to Research on Cigarette Smoke, and (8) References.

MECHANISMS OF DEPOSITION

The mechanisms involved in the deposition and retention of inhaled particles are related to the physical and chemical properties of the dust as well as to the anatomy and physiology of the respiratory tract. Both theoretical and experimental considerations have shown that particles are deposited in the respiratory tract by one of the following three mechanisms.

1. Inertial Impaction. A particle suspended in an air stream is not able to follow the stream because of its inertia as it moves through the passages of the respiratory tract and is deposited against the walls of the passage. Inertial impaction is an important mechanism in the nasal airways and in the upper lung where the air velocity is fairly high. Landahl and Herrman,[26]*, May[32], and Rosin and co-workers[42] have studied the deposition of particles in curved tubes and have shown that the larger particles are likely to be separated by this mechanism. The inertial effect on the particles is directly proportional to the density and to the square of the particle diameter.

2. Sedimentation. Because of gravitational effects, a particle will settle downward. This mechanism is one of the more important causes of deposition of larger particles in the deeper portion of the lungs where the air velocity has been reduced. Sedimentation rate also is proportional to the density and to the square of the particle diameter; therefore, the more massive particles that have survived the inertial influence in the upper respiratory tract will be deposited by sedimentation. The settling rate for small particles can be calculated from Stokes' law.

3. Brownian Motion. In the alveolar sacs where the air velocity is quite low, Brownian motion becomes an important mechanism in the removal of particulate matter. Very small particles suspended in air are in continuous motion because of being bombarded by air molecules. The mean displacement after a given time can be computed from Einstein's[17] diffusion equation. From this equation it is then possible to calculate the rate of removal of particles by diffusion.

Findeisen[19] in his theoretical study of deposition applied all three of the above mechanisms to determine deposition of particles in the bronchial tree.

METHODS OF PRODUCING AEROSOLS FOR EXPERIMENTAL STUDIES

The most common method of producing an aerosol for retention studies is by dispersion of dusts or atomization of test liquids, as was done by Morrow and Gibb[36], Landahl and Black[25], Dautrebande and co-workers[13,14], Palm[39], and others. The particle-size distribution of the aerosols produced by this method of generation is very broad, and it is difficult to interpret the retention data. For most of these experiments, the retention is plotted as a function of the number or mass median diameter. Brown[7] also produced dust aerosols by dispersing preclassified solid materials suspended in a water solution by means of a nebulizer. The droplets containing the particulate matter were dried before sampling.

The studies most applicable to this survey on retention in the respiratory tract are those made by Altshuler and co-workers[1], Wilson and LaMer[54], and Landahl and co-workers[27,29], using monodispersed aerosols. The monodispersed aerosols were produced by the careful control of condensation of the test liquid on condensation nuclei. The advantages of using homogeneous or monodispersed aerosols are that the particles are nearly uniform in size and their diameter is therefore easily measured. When a polydispersed aerosol is inhaled, the distribution of sizes obscures the relationship between particle size and retention.

*References appear on page 19.

Buckland and co-workers[9] also produced monodispersed aerosols, by the atomization of slurries of Bacillus subtilus spores tagged with radioactive phosphorus. After the liquid evaporated, the aerosol was composed of uniformly sized spores about 1 micron in diameter. Goldberg and Leif[21] produced aerosols of Pasteurella pestis bacteria which had been tagged with radioactive phosphorus. The diameter of the aerosol particles formed was also 1 micron.

THEORETICAL STUDIES OF DEPOSITION IN MAN

The use of models for estimating the deposition of particulate matter in the respiratory tract has been discussed by Trunit[48], Findeisen[19], Hatch and Hemeon[23], Davies[15], Berghaus[6], Eisenbud[18], Wilson[53], and Landahl[28]. One of the best known treatments was presented by Findeisen who made the following simplifying assumptions:

(1) The breathing passages were assumed to be straight tubes of which the length, width, and position were approximately in accordance with anatomical data. The alveolar sacs were assumed to be hollow spheres.

(2) Inhalation and exhalation were assumed to take place at equal and constant rates of 200 cubic centimeters per second for a time cycle of 2 seconds without any pause between inhaling and exhaling.

(3) Sedimentation and diffusion mechanisms of deposition in the breathing passages were considered, as well as initial deposition at branching points of the passages. Deposition in both inhaling and exhaling was taken into account.

From these assumptions, Findeisen computed the percentage of particles of a given size that would deposit in each of the portions of the breathing system. Since he assumed that the air-flow velocity is constant over the cross section of the air ducts, he should have obtained efficiency values that were too high.

Landahl[28] modified Findeisen's calculations, using essentially the same model and changing the flow rate to 300 cc/sec with three cycles of 4, 8, and 12 seconds to give total volumes of 450, 900, and 1350 cc. A calculation was also made with a flow rate of 1000 cc/sec with a 4-second cycle and a total volume of 1500 cc.

Table 1 is a schematic representation of the respiratory tract used by Landahl. Using these dimensions, Landahl made more detailed calculations than Findeisen and determined the fraction of air-borne particles retained in the various regions of the respiratory tract. Special consideration was given to the effect of deep and shallow breathing.

Table 2 summarizes the results of the relative amounts of various sized particles deposited in different regions of the respiratory tract under selected conditions.

TABLE 1. LANDAHL'S SCHEMATIC REPRESENTATION OF RESPIRATORY TRACT

Region	Number	Volume, cc	Relative Volume	Diameter, cm	Length, cm	Cross-Section Area, cm^2	Velocity, cm/sec	Passage Time (A), sec	Fraction Passing (B)	(A x B)
Mouth	1	20	0.04	2	7	3	100	0.07	1.00	0.07
Pharynx	1	20	0.04	3	3	7	45[(a)]	0.07	0.96	0.06
Trachea	1	25	0.06	1.6	12	2	150	0.08	0.92	0.074
Primary bronchi	2	10	0.02	1.0	6	0.8	190	0.032	0.86	0.027
Secondary bronchi	12	4	0.01	0.4	3	0.12	210	0.014	0.84	0.012
Tertiary bronchi	100	5	0.01	0.2	1.5	0.03	100	0.015	0.83	0.012
Quaternary bronchi	770	7	0.015	0.15	0.5	0.018	22	0.023	0.82	0.02
Terminal bronchioles	$6x10^4$	50	0.11	0.06	0.3	$2.8x10^{-3}$	1.8	0.17	0.81	0.14
Respiratory bronchioles	$1.5x10^5$	30	0.06	0.04	0.15	$1.2x10^{-3}$	1.7	0.09	0.70	0.06
Alveolar ducts I	$3x10^6$	100	0.22	0.03	0.05	$7x10^{-4}$	0.14	0.36	0.64	0.25
Alveolar ducts II	$4x10^7$	600	0.42	0.025	0.03	$4.9x10^{-4}$	0.015	2.0	0.42	0.83
Alveolar sacs	10^8	2000	0	0.033	0.033		0			

(a) Glottis velocity = 150

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TABLE 2. PER CENT RETENTION IN VARIOUS REGIONS OF THE RESPIRATORY TRACT AS CALCULATED BY LANDAHL

	300 CC/Sec, 4-Sec Cycle, 450 CC Tidal Air					300 CC/Sec, 8-Sec Cycle, 900 CC Tidal Air					300 CC/Sec, 12-Sec Cycle, 1350 CC Tidal Air					1000 CC/Sec, 4-Sec Cycle, 1500 CC Tidal Air				
	Particle Diam, μ					Particle Diam, μ					Particle Diam, μ					Particle Diam, μ				
Region	20	6	2	0.6	0.2	20	6	2	0.6	0.2	20	6	2	0.6	0.2	20	6	2	0.6	0.2
Mouth	15	0	0	0	0	14	1	0	0	0	14	1	0	0	0	18	1	0	0	0
Pharynx	8	0	0	0	0	8	1	0	0	0	8	1	0	0	0	10	1	0	0	0
Trachea	10	1	0	0	0	11	1	0	0	0	11	1	0	0	0	19	3	0	0	0
Primary bronchi	12	2	0	0	0	13	2	0	0	0	13	1	0	0	0	20	5	0	0	0
Secondary bronchi	19	4	0	0	0	17	4	1	0	0	18	5	1	0	0	21	12	3	0	0
Tertiary bronchi	17	9	0	0	0	20	9	1	0	0	21	10	1	0	0	9	20	4	1	0
Quaternary bronchi	6	7	1	0	0	8	7	1	0	0	8	7	1	0	1	1	10	2	0	0
Terminal bronchioles	6	19	4	2	2	6	24	6	2	2	6	24	6	1	2	1	9	2	0	0
Respiratory bronchioles	0	11	4	2	2	0	10	4	2	2	0	12	4	2	2	0	3	1	2	2
Alveolar ducts I	0	25	16	5	6	0	27	19	7	9	0	27	20	8	8	0	13	10	4	5
Alveolar ducts II	0	5	28	10	9	0	5	48	21	18	0	5	49	24	23	0	17	41	16	14
Alveolar sacs	0	5	0	0	0	0	0	0	0	0	0	0	5	8	7	0	1	7	5	7
Total	93	83	51	19	19	97	91	80	32	31	99	94	87	43	43	98	95	70	28	28

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Figure 1 is a schematic representation of the anatomy of the pulmonary tree showing the results of Landahl. This illustration indicates that particles 20 microns and larger are removed completely before they leave the terminal bronchioles. The majority of the particles 6 microns in diameter are removed before they reach the lower alveolar ducts, and almost all of the particles of 2.0-micron size and greater are removed in the lower alveolar ducts. Landahl's calculations show substantially no removal of particles of any size by the alveolar sacs, whereas Findeisen showed as much as 45 per cent removal of 2.0-micron particles.

The difference in results between these two theoretical studies can probably be attributed to the difference in the assumed volume of the alveolar sacs.

EXPERIMENTAL STUDIES OF DEPOSITION IN MAN

The amount of material that deposits in the respiratory system and the depth to which it penetrates before deposition are functions of particle size. Therefore, considerable attention has been given to determining exactly how the two variables are related. Experiments were conducted with naturally occurring dusts, and with homogeneous or heterogeneous aerosols produced in the laboratory.

Deposition of Naturally Occurring Dusts

Disease has been attributed to dusts since ancient times. One of the first references to disease caused by dust and fumes appears in the writing in the First Century A. D. by Plenius[40] who described the devices used by ore refiners to prevent the breathing of "fatal dusts".

The majority of the information on deposition of naturally occurring dusts in the lungs arises from histological studies. Information on chronic exposure can be found in studies by Gessner and co-workers[20], Bedford and Warner[5], Brown[7], Thomas and Stegemann[47], Moir[34], and McCrae[33]. By comparing the size distribution of dust found in the lungs to that found in the exposure site, a rough estimate can be made of the retention of insoluble particles. This technique is seriously affected by the ciliary cleansing action of the bronchial tree.

The studies by van Wijk and Patterson[49] were carried out underground in a gold mine where natural dusts of quartzite were being generated. They used two thermal precipitators to collect a sample before and after inhalation. For these experiments, the test subject breathed through the apparatus for about 10 minutes to allow his lungs to come to equilibrium with the dusty air. The inhaled and exhaled samples were then collected for a period of about 20 minutes. The particle-size distribution of the collected particles was then determined with a microscope fitted with a specially calibrated graticule.

Table 3 summarizes the results of the retention trials for 40 distinct experiments. This table shows the average percentage of particles of the various diameters removed.

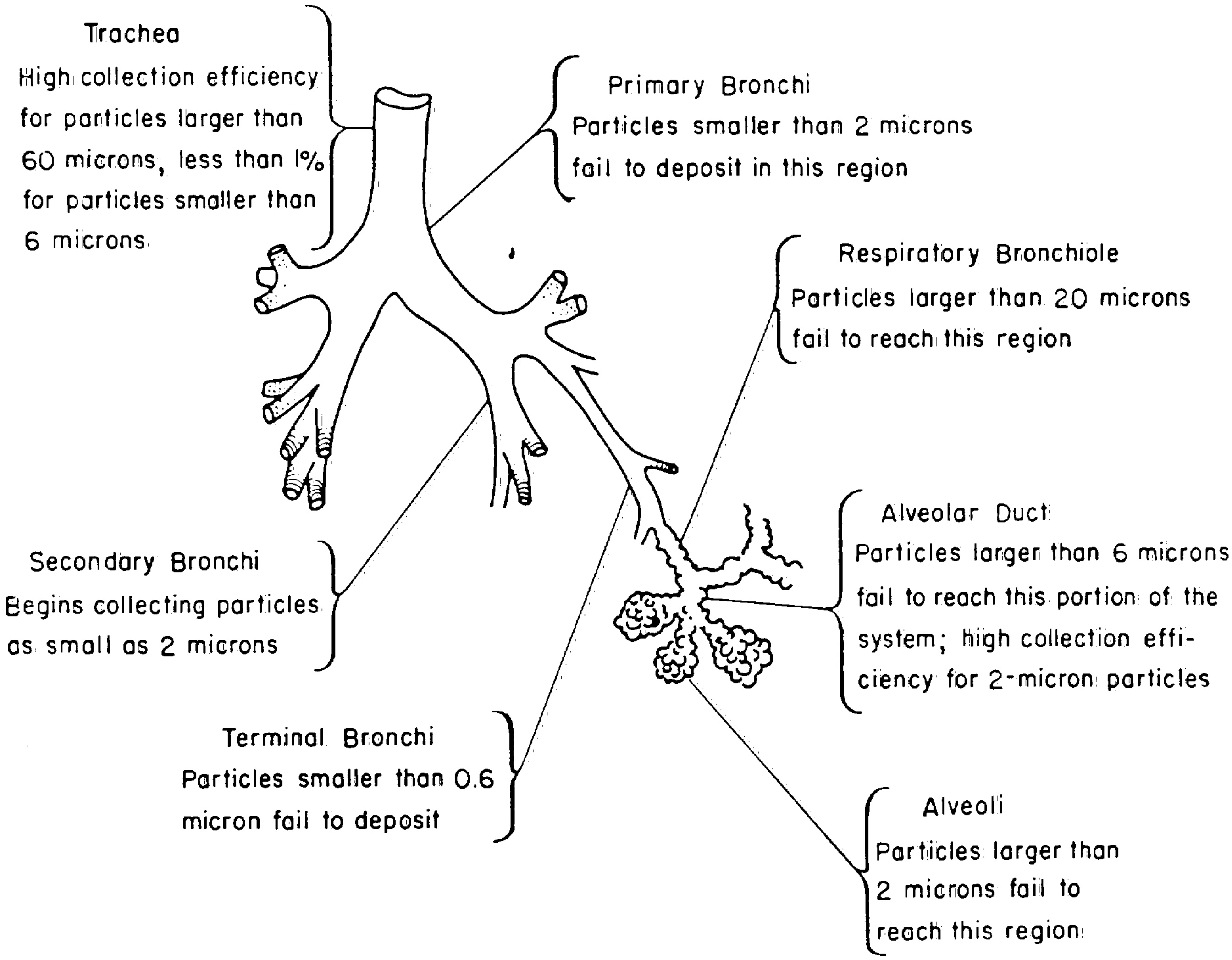

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FIGURE 1. SCHEMATIC REPRESENTATION OF THE ANATOMY OF THE PULMONARY TREE SHOWING THEORETICAL DEPOSITION COMPUTED BY LANDAHL

TABLE 3. RETENTION OF QUARTZITE DUST AS A FUNCTION OF PARTICLE SIZE IN THE RESPIRATORY TRACT

Van Wijk and Patterson(49)

Apparent Diameter of Particle, microns	Equivalent Particle Diameter, microns ($\rho^{1/2}D_p$)	Percentage Removed by Breathing
>0.2	>0.3	21.0
0.2	0.3	27.8
0.4	0.6	37.8
0.8	1.3	52.8
1.2	1.9	63.0
1.6	2.6	76.3
2.0	3.2	79.5
2.5	4.0	84.7
3.0	4.8	89.4
4.0	6.5	96.1
5.0	8.1	92.6

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These results fail to show a minimum of deposition in the 0.4-micron range; however, the high percentage of retention for the larger sizes is in good agreement with the theoretical predictions.

Deposition of Heterogeneous Experimental Aerosols

Many data on the retention of aerosols in the respiratory tract have been obtained with heterogeneous aerosols because they are so easily generated. Most of these aerosols were produced by the direct atomization of dry powders, solutions, slurries, or pure liquids. The particle-size distribution of this type of aerosol is quite broad, and a considerable amount of information is lost when an "average" diameter is used to represent the size distribution of the aerosol. Important studies using their technique have been reported by Brown and co-workers[8], Landahl and co-workers[25, 26], Lehman and co-workers[30], Lehmann[31], Milburn and co-workers[35], Worth and Schiller[55], Dautrebande and co-workers[12, 13, 14], Drinker and co-workers[16], Davies[15], and Morrow and Gibb[36].

In the studies by Dautrebande and co-workers[14], the aerosol was partially classified by passing it through scrubbers before inhalation to remove the larger particles. The particulates used by Brown and co-workers[8] were classified into very narrow size bands before dissemination to produce aerosols.

Figure 2 is a summary of 100 tests by Brown using nasal inhalation techniques for clay dust particles having number median diameters from 0.24 to more than 5 microns. This figure shows that upper respiratory retention is about 85 per cent for particles 5 microns in diameter and drops off to zero for particles about 1 micron in diameter. The curve for measured retention is very similar to that obtained by van Wijk and Patterson[49]. The curve for alveolar retentions shows that more than 90 per cent of the 1 to 5-micron particles which pass the upper respiratory tract are retained in the alveolar region.

Figure 3 is a plot of the percentage deposition of inhaled dust in the upper respiratory tract and alveoli in relation to particle size. The data for this curve were calculated from the data in Figure 2. The main conclusion drawn from these curves is that the optimum equivalent particle size for maximum alveolar deposition is approximately 2 microns.

Brown's experimental size range did not include particles smaller than about 1/4 micron. If the density factor is considered, the smallest equivalent particle diameter becomes about 0.4 micron, which is essentially the critical size for minimum retention obtained by other experimenters.

Morrow and Gibb[36] determined the deposition of submicronic aerosols of sodium chloride. The particles had a number median diameter of 0.052 micron and a geometric standard deviation of 2.26. The results of these experiments indicate 63 per cent retention. No attempts were made to determine how hygroscopicity may cause the particle diameter to change after inhalation into the lungs where the humidity is nearly 100 per cent.

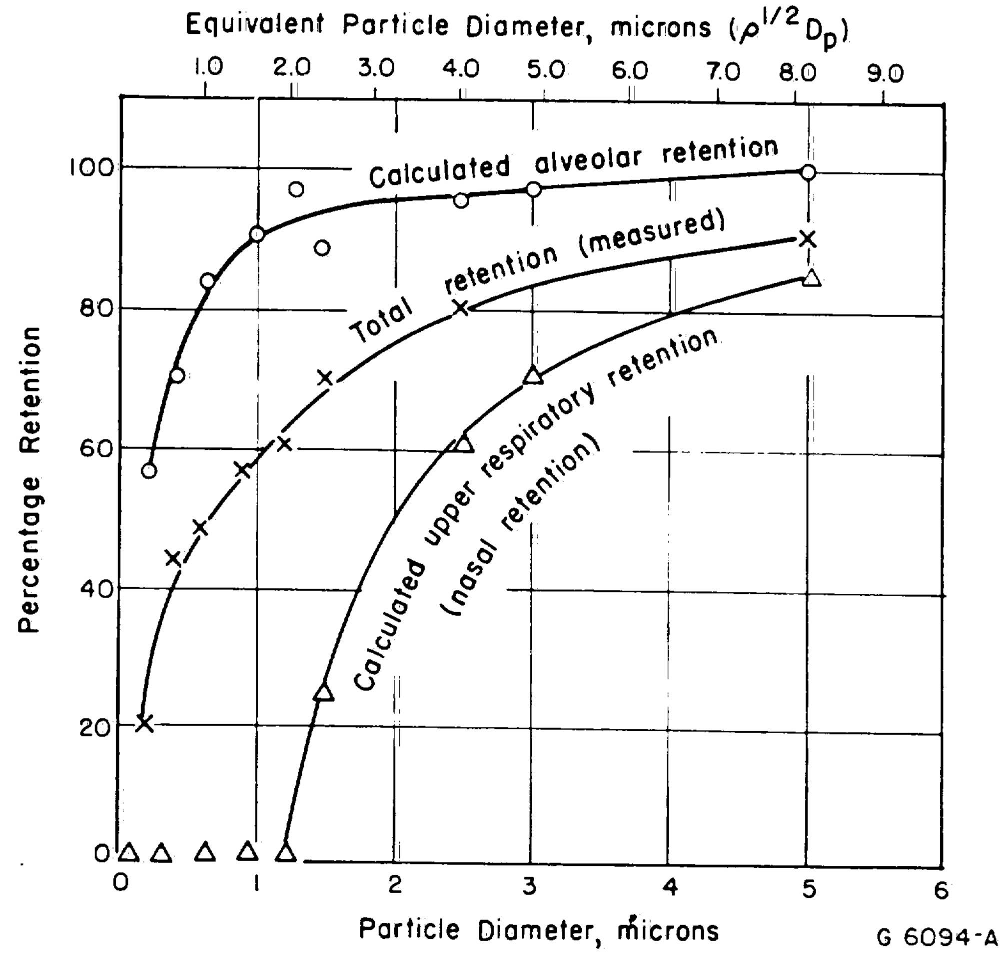

FIGURE 2. LUNG RETENTION OF CLAY DUSTS AS A FUNCTION OF PARTICLE SIZE

(Brown, J. H., et al)[8]

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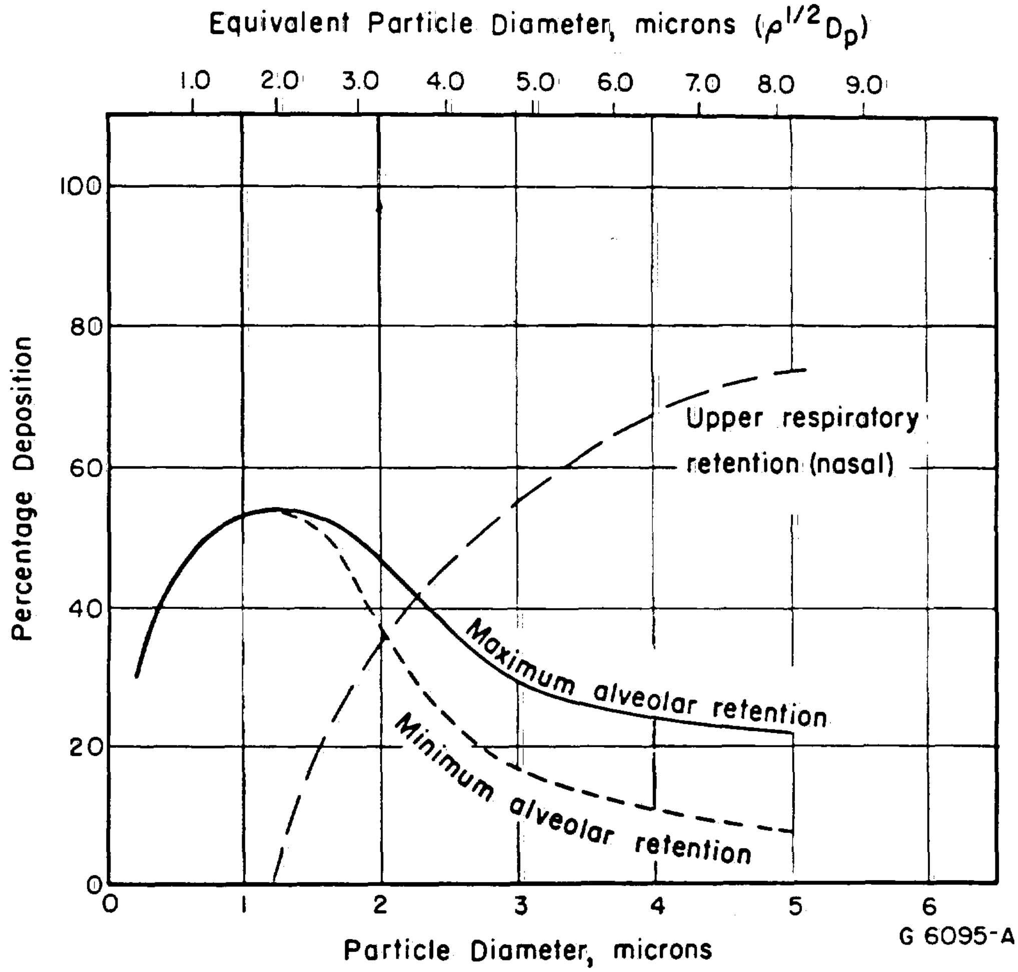

FIGURE 3. THEORETICAL DEPOSITION OF CLAY DUSTS IN THE UPPER RESPIRATORY TRACT AND ALVEOLI

(Brown, J. H., et al)[8]

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In the studies of Landahl and Herrman[26], and others who used cascade impactors for sampling aerosols before and after inhalation, the retention was based on the classified fractions in the device. Thus, the particle-size distribution for each fraction was fairly narrow. However, the distribution was still broad enough to obscure any abrupt change in the relationship between particle size and retention. This difficulty can be eliminated by the use of monodispersed aerosols.

Deposition of Monodispersed Aerosols

Monodispersed aerosols are aerosols in which all the particles are of the same size. It is possible to produce nearly monodispersed aerosols by the atomization of extremely dilute slurries of carefully prepared uniformly sized polystyrene beads and certain species of bacteria and spores. Mists of a high degree of uniformity can also be produced by a LaMer-type[46] generator. The most accurate data concerning respiratory retention have been obtained by Wilson and LaMer[54], Altshuler and co-workers[1], and Landahl and co-workers[27,29], using monodispersed aerosols produced in a LaMer generator.

Wilson and LaMer produced glycerol aerosols on condensation nuclei of radioactive sodium chloride. The droplets were then diluted to 50 per cent glycerol by volume by passing the aerosol through a conditioning chamber containing an equivolume glycerol-water solution. After the aerosol had come to equilibrium, the output rate was measured by collecting a sample on a filter. The test subject was then allowed to inspire the aerosol by a mouthpiece, and the amount of material exhaled was collected on a filter. After correcting for losses in the tubing, it was then possible to calculate the retention rate for various particle sizes.

For these tests no correction was made for the growth of the aerosol particles by absorption of water vapor from the saturated air in the lungs. Because of the highly hygroscopic nature of this type of aerosol, it will continue to grow as long as it is in contact with the humid atmosphere of the lungs. By assuming that the aerosol comes to equilibrium at only 97 per cent humidity within the lungs, the particles will increase in diameter by 53 per cent, which appears to be a more realistic increase than the 20 per cent predicted by the experimenters.

In addition to measuring the total retention directly, an estimate of the amount of alveolar retention was made by placing a Geiger-Mueller counter against the chests of the test subjects. The radiation intensity detected by the counter is a close approximation to the quantity of aerosol deposited in the finer respiratory passages.

Figure 4 is a plot of the average relative auxiliary radiation counts, recorded in the chest region under the armpits, as a function of particle diameter. This figure shows that the most effective size range for deposition in the alveoli is between 0.6 and 2.4 microns in diameter. The curve also has a double peak which suggests that the upper respiratory tract exerts a maximum filtering efficiency at some particular size producing a minimum of alveolar retention for that size.

In the studies by Altshuler and co-workers[1], monodispersed aerosols of triphenyl phosphate were used. Triphenyl phosphate was chosen as the test material

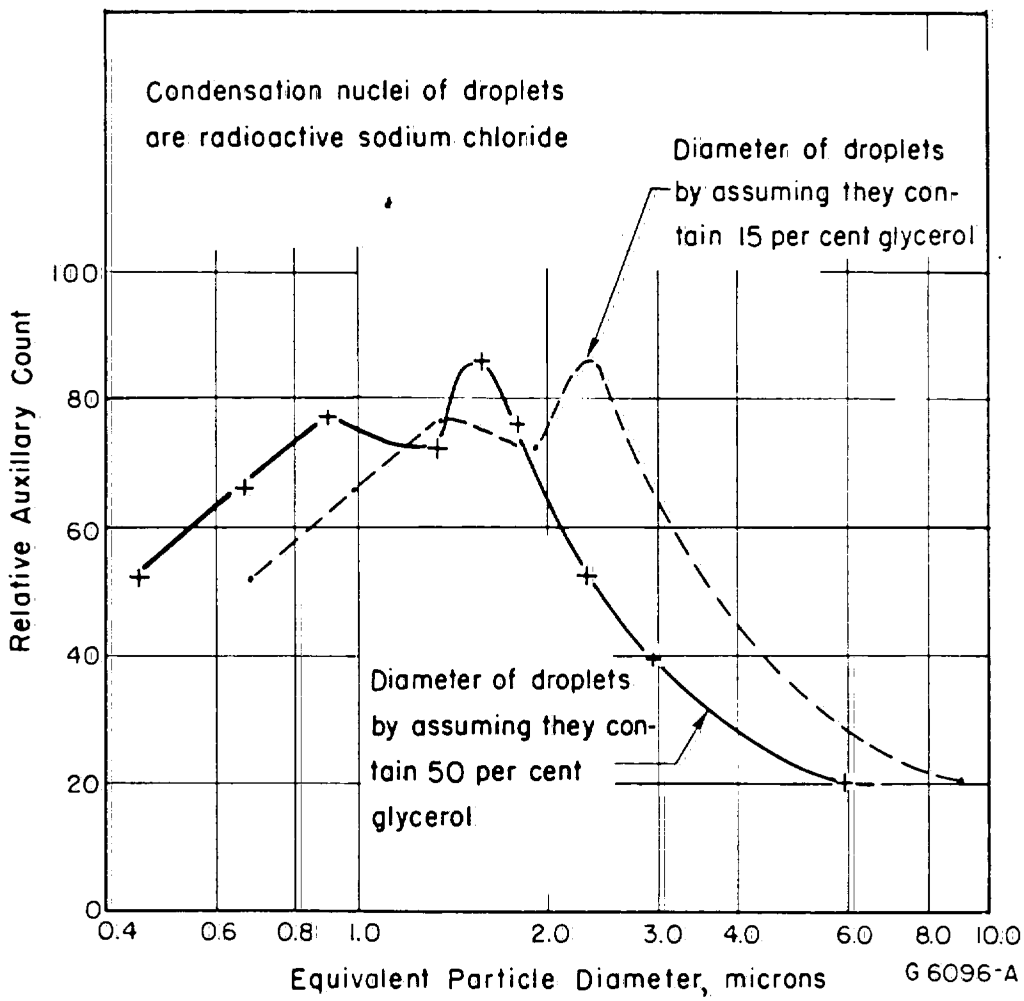

FIGURE 4. AVERAGE RELATIVE AUXILLARY RADIOACTIVE COUNTS AS A FUNCTION OF EQUIVALENT PARTICLE DIAMETER OBTAINED BY WILSON & LAMER

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because it met the requirements of the generator, it is not very toxic, and it is non-hygroscopic. The size of the particles used was varied from 0.14 to 3.2 microns covering the region of minimum deposition. The particle-size measurements were made with the microscope, by determining terminal velocity for free fall, and with the tyndallometer.

Figure 5 is a summary of the retention data obtained for three different test subjects and three different respiratory rates. This figure shows a definite minimum of deposition in the neighborhood of 0.4 micron which was predicted by Findeisen. This figure also shows a greater deposition for slow deep breathing than for the shallow fast breathing. The effect of breathing rate is much more pronounced for the large 1.6-micron particles than for the small 0.14-micron particles. For the larger particles, the mechanism of removal is sedimentation which is a function of the first power of residence time whereas, for the smaller particles, the mechanism of removal is Brownian motion which is related to the square root of residence time.

Landahl and co-workers(27) used monodispersed aerosols of tricresyl phosphate in their retention studies. The range of equivalent particle diameters, corrected to unit density, varied from 0.11 to 6.3 microns. The results of their tests also show a definite minimum of deposition in the 1/2-micron range.

In these studies, an effort was made to determine the variability of retention of the aerosol particles by different subjects. A total of 21 male and 3 female subjects participated. The diameter of the uniformly sized droplets was 0.25 micron. The breathing cycle was 12 seconds and the tidal volume was 1350 cc at a rate of 300 cc per second. The average retention was 41 per cent, with a standard deviation of 5.1 per cent.

In addition to determining the retention as a function of particle size, Landahl and co-workers also studied the effect of respiration pattern and residence time on retention.

Retention for Various Patterns of Respiration and Residence Time

An important variable in the retention of particulate matter in the respiratory tree is the length of time the particles remain in the system. Those particles which are first to enter the respiratory tract are the last to leave during exhalation. Similarly, the last particles to enter the system are the first to leave. Landahl and co-workers have determined the fraction of particulates expired for five different breathing patterns. Three of the patterns were at a breathing rate of 18 liters per minute, and the remainder were at a rate of 60 liters per minute.

Figure 6 summarizes the results obtained at a breathing rate of 18 liters per minute. These figures show that there is little loss of the smaller particles in the first fraction of expired air. Similar results were obtained at a flow rate 60 liters per minute. At the same respiratory pattern as the low flow rate, the retention was slightly higher.

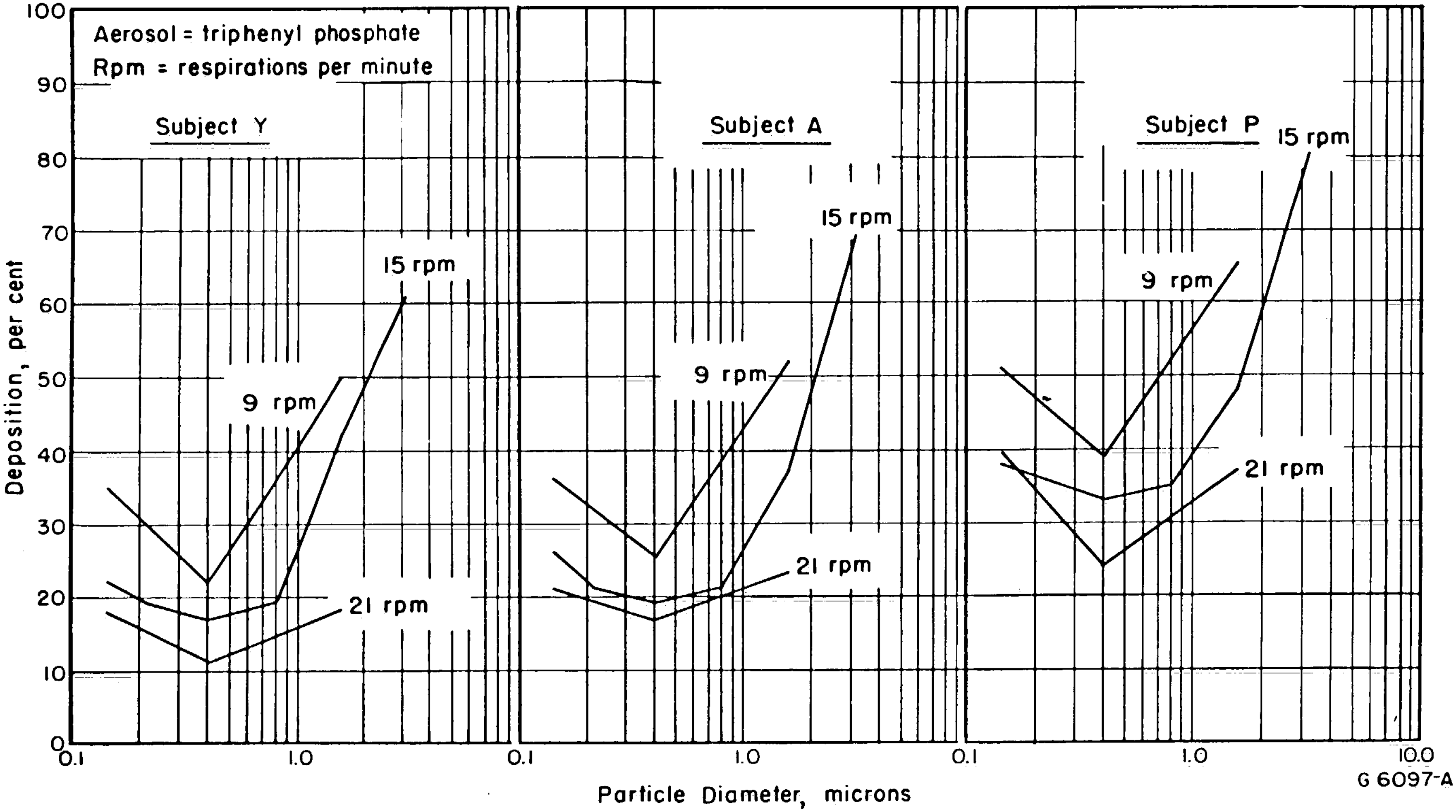

FIGURE 5. LUNG RETENTION AS A FUNCTION OF PARTICLE SIZE AND RESPIRATION RATE (Altshuler and Co-workers)[1]

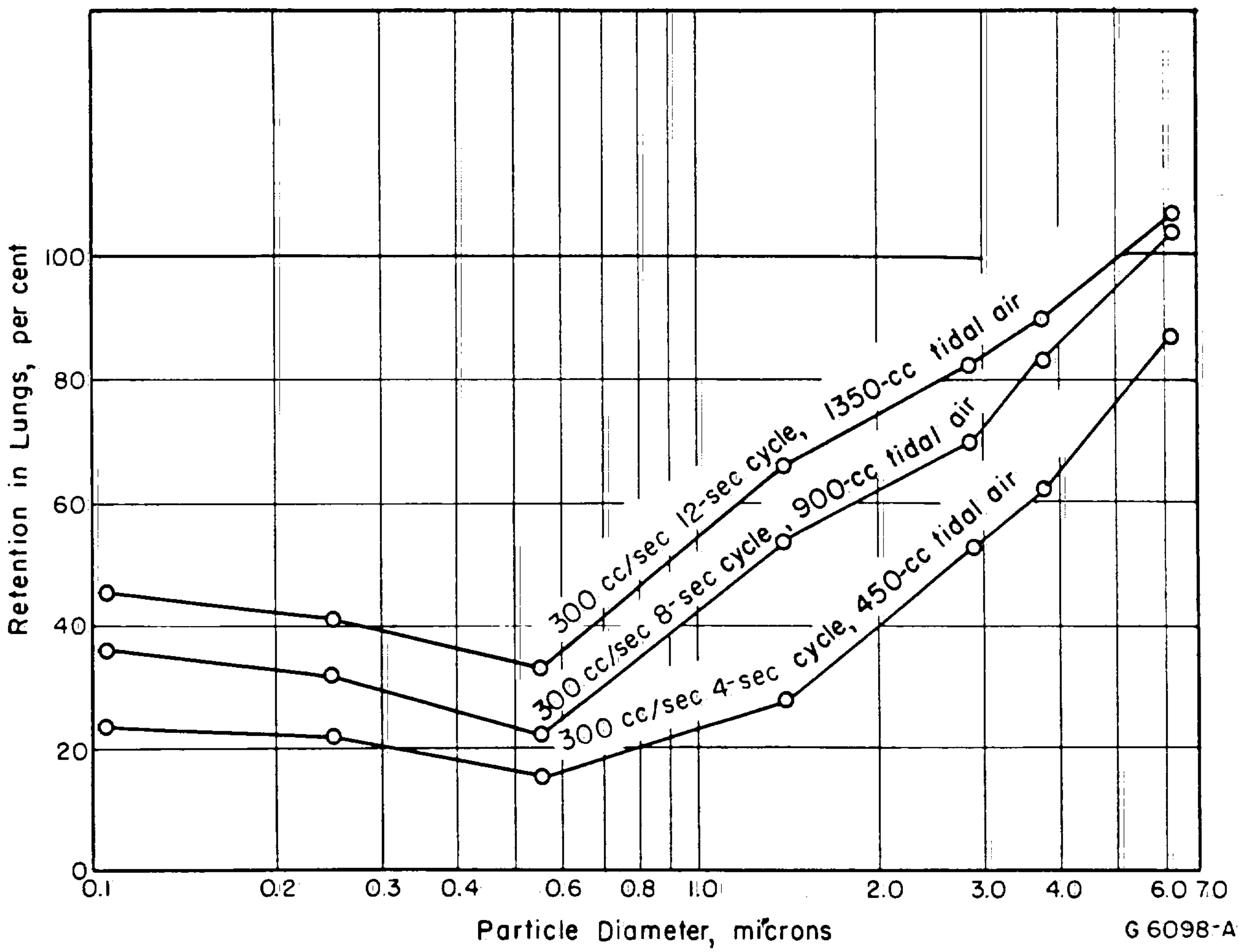

FIGURE 6. LUNG RETENTION AS A FUNCTION OF PARTICLE SIZE AND RESPIRATION RATE

(Altshuler and Co-workers)[1]

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EXPERIMENTAL STUDIES OF DEPOSITION IN ANIMALS

Animals have played an important role in medical research on lung retention because histologic studies can be made immediately after exposure. Also, the effects of materials on lung tissue which would be too dangerous for human inhalation can be studied. Some of the long list of papers that deal with inhalation studies in animals are those of Cauer and Neymann(10), Neymann(38), Beckman(4), Goldberg and Leif(21), Scott and co-workers(43,44), Barrett and co-workers(3), Verzar and co-workers(50), Hatch and Kindsvatter(22), Shoshkes and co-workers(45), Asset and co-workers(2), Punte(41), Cohn and co-workers(11), Buckland and co-workers(9), Ishikawa and Drinker(24), Wilson and co-workers(51,52), Morrow and Gibb(37), and Palm and co-workers(39).

To evaluate the results of animal inhalation studies as related to the retention in man, a direct comparison must be made between man and the animal using the same aerosol. In a recent study by Morrow and Gibb(37), such a comparison was made between man and dog, with submicronic aerosols of sodium chloride. The results of these studies showed that the dog should be considered to be especially appropriate for investigations in the field of inhalation toxicology. For an aerosol with a number median diameter of 0.04 micron, average retention was 66.5 per cent for dogs, compared with 63.4 per cent for man.

Palm and co-workers(39) determined the retention of particulate matter in the respiratory tract for guinea pigs and monkeys. They present their data in a form such that they can be compared directly with those for man. From this work, it can be concluded that (1) the smaller the animal the greater is the over-all retention for a given particle size, (2) alveolar efficiency of animals was not significantly different than that of man, (3) the particle size for which data on man and animals compare most favoarbly was found to be 1 micron, and the percentage deposition was about 50 per cent, and (4) the agreement of the retention data between man and monkey was better than between man and guinea pig.

Because the agreement for the retention data between the experimental animals and man is best for 1-micron particles, aerosols for comparative tests should be comprised of uniformly sized particles about 1 micron in diameter.

SUMMARY OF RESULTS

There is considerable disagreement among the various investigators of particle retention in the lungs. The two major causes of lack of agreement are (1) failure to use a uniform breathing rate, and (2) the use of a mean particle size to describe a test aerosol which had a wide size distribution.

Figure 7 is a plot showing total retention in the respiratory tract by mouth breathing as a function of equivalent particle diameter ($\rho^{1/2}D_p$). This plot shows the results obtained with monodispersed aerosols by Altshuler, Landahl, and Wilson. Also shown in this figure are the theoretical results obtained by Landahl and the alveolar retention obtained by Wilson and LaMer based on radio-active measurements.

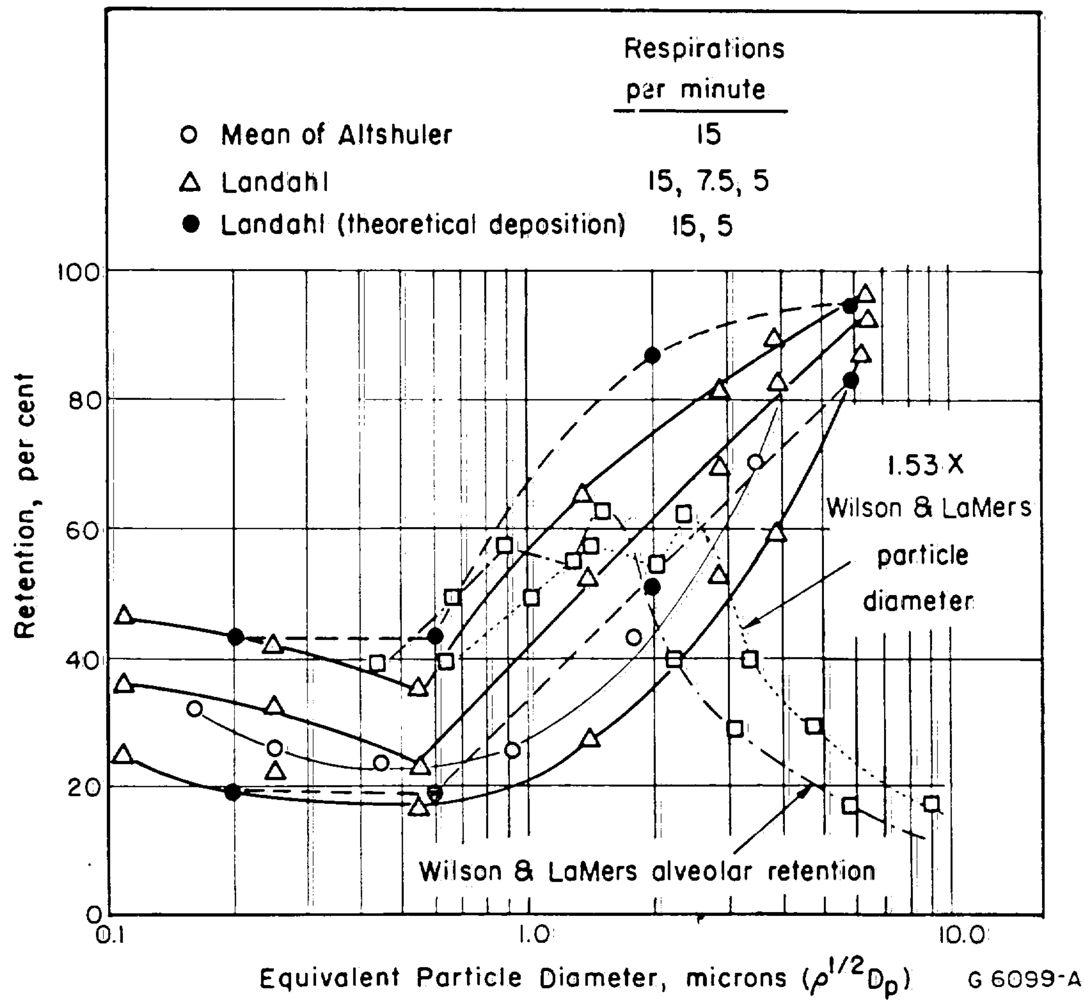

FIGURE 7. COMPARISON OF LUNG RETENTION DATA OBTAINED BY THREE DIFFERENT INVESTIGATORS

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Both the experimental and theoretical results show a minimum of retention in the 0.4 to 0.6-micron range. All the data also indicate 90 per cent or more retention of particles greater than 7 microns. In addition to particle size, the next largest variable affecting retention is breathing rate. The theoretical calculations of Landahl agree well with the experimental results obtained by Landahl and co-workers, except for particles in the 2-micron range. For this size, the theoretical calculations are too high at both breathing rates.

The use of radioactive sodium chloride to obtain an approximation of alveolar retention gives an excellent measurement for therapeutic application of aerosols in the smaller branches, bronchioles, and alveoli. To establish definitely the particle size for maximum retention, the experiments should be repeated using a nonhygroscopic carrier. The results of the glycerol-water aerosols indicate the maximum occurs for particles which have a equivalent diameter of 1.5 microns. By assuming that the particles grow until they contain 85 per cent water, the diameter for the maximum would increase only to 2.3 microns.

POSSIBLE APPLICATION OF LUNG-RETENTION SURVEY TO RESEARCH ON CIGARETTE SMOKE

A specific application of this literature survey to research on cigarette smoke is the possibility of designing a cigarette which will produce a smoke with a minimum amount of deposition in that portion of the respiratory tract that is most sensitive to the undesirable effects of smoke particles. Because nicotine must be retained in the respiratory system for the smoker to obtain the physiological benefit from smoking, it may be desirable to alter the size distribution of the smoke particles before they leave the cigarette to control the region of the respiratory tract in which they are deposited. Basic data on lung retention of cigarette smoke should serve as a guide during studies to control the size distribution of smoke as it enters the smoker's mouth.

Assuming that the ideal particle size from the standpoint of lung retention could be produced, the problem of taste probably could be resolved by proper blending of casing agents and cigarette tobacco.

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